PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 244-204-WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/050427	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 10.04.2003

International Patent Classification (IPC) or national classification and IPC
C07D235/06, C07D401/10, A61K31/4184, A61K31/454, A61K31/496, A61P21/02, A61P23/00, A61P25/08, A61P25/20, A61P25/22

Applicant
NEUROSEARCH A/S et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.01.2005	07.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050427

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-33 as originally filed

   Claims, Numbers

   1-12 as originally filed

   Claims, Pages

   34-36 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12

because:

☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050427

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/50057 A (TEUBER LENE ; WAETJEN FRANK (DK); NEUROSEARCH AS (DK)) 27 June 2002 (2002-06-27)

D2: WO 00/78728 A (TEUBER LENE ; WAETJEN FRANK (DK); NEUROSEARCH AS (DK)) 28 December 2000 (2000-12-28)

D3: WO 98/17651 A (TEUBER LENE ; WAETJEN FRANK (DK); NEUROSEARCH AS (DK)) 30 April 1998 (1998-04-30)

The application relates to benzimidazole derivatives useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex.

1) Article 33(2) PCT

All three of the above cited in the Search report documents disclose the 5-alkoxycarbonyl-2-[(1-piperazinyl/piperidinyl)-phenyl]-benzimidazole core structure in compounds useful as $GABA_A$ receptor modulators.

The compounds of D1 differ from the claimed entities in that the piperidine, piperazine or homopiperazine moiety is substituted by a carboxymethyl or amidomethyl group. In D2 the "heterocycle", defined as piperazin-1-yl, homopiperazin-1-yl, piperidin-4-yl etc. in claim 8, can be substituted with an alkoxyalkyl group (claim 1: page 88, line 31). In D3 the "heterocycle", defined as piperazin-1-yl, homopiperazin-1-yl or piperidin-4-yl etc. in claims 6-8, can be substituted with an alkenyl or alkylcarbonylalkyl group (claim 1: page 72, lines 1-10). On the basis of the definition of the substitution pattern of the heterocyclic moiety in documents **D2**

and D3, their subject-matter is considered to overlap with that of the present application.

However, due to the absence of explicit compounds of D2 or D3 falling under the definition of the claimed entities, the present claimed subject-matter can be considered as **formally** novel under Article 33(2) PCT.

2) Article 33(3) PCT

a) As closest prior art may be considered any of the documents D2 or D3, because -similar to the present application- each one of them discloses the 5-alkoxycarbonyl-2-[(1-piperazinyl/piperidinyl)-phenyl]-benzimidazole core structure in compounds useful as $GABA_A$ receptor modulators.

The objective problem underlying the present application is thus "the provision of further compounds useful as $GABA_A$ receptor modulators".

According to the present application the solution to the above problem lies in the substitution of the piperazinyl/piperidinyl moiety with an alkoxyalkyl, alkoxyalkenyl, alkoxyalkynyl, alkylcarbonylalkyl, alkenyl or alkynyl group. However, D2 discloses the alkoxyalkyl substitution (claim 1: page 88, line 31) of the heterocycle, which is defined in claim 8 as piperazin-1-yl, homopiperazin-1-yl, piperidin-4-yl etc., whereas an aryl-alkyloxyalkyl substitution is explicitly diclosed in compound 1v of table 1 . Furthermore, D3 discloses the alkenyl and alkylcarbonylalkyl substitution (claim 1: page 72, lines 1-10) of the heterocycle, which is defined in claims 6-8 as piperazin-1-yl, homopiperazin-1-yl or piperidin-4-yl etc..

Due to the disclosure of documents D2 and D3 the subject matter of the present application can not be considered as inventive under Article 33(3) PCT.

Furthermore, even when regarding the application as a selection invention over the prior art, inventive merit can not be acknowledged, as no data are given, which could present possible unexpected effects or properties of the selected substitution pattern in relation to the rest of the range.

b) For the assessment of the present claim 12 (see also: description page 16, lines 18-35) on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

a) No examples support the definition of n being 2.

b) With respect to claims 10 and 12, and even if claim 12 will be reformulated to a Swiss Type Form claim by entering the European Phase, it must be also mentioned, that they can not be considered:

I) as industrial applicable as the modulation of the GABA receptor complex can not be considered in itself as a therapeutic application. The discovery, that a substance selectively modulates the GABA receptor complex, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art and

ii) as clear (Article 6 PCT), since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition e.g. any condition susceptible of being improved or prevented by the modulation of the GABA receptor complex, and accordingly within the scope of the claim.

The reason for the necessity of this clarification is, that a claim referring to a condition to be treated, which is functionally defined, would not be limited to the treatment of said specified condition (here central nervous system diseases and disorders), but by contrast embraces an undefined number of conditions all allegedly capable of being improved or prevented by the modulation of the GABA receptor complex. Under these circumstances the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition not expressly filed in the application but nevertheless affected by the administration of the said compounds is comprised in the scope of the claim.

c) The term "prodrug" mentioned in page 9, lines 8-11 leads to an unclear scope, since it is unclear which structures are intended. The expression "prodrug" includes compounds obtained from another compound by a chemical reaction (structures which are structurally remote from the starting material), functional derivatives (compounds wherein the heteroatoms

are exchanged by alternative atoms), compounds with numerous different types of side groups etc. Therefore, such a formulation is to be excised.